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(54) Sustained absorption pharmaceutical composition.

(57) A sustained absorption theophylline-containing pellet for oral administrattion comprises a core of theophylline or a pharmacological equivalent thereof and an organic acid embedded in a polymeric material in a multilayer arrangement and an outer membrane which permits release of the theophylline at a controlled rate in an aqueous medium. The pellet has a dissolution rate in vitro in an aqueous medium, which when measured in a basket assembly according to U.S. Pharmacopoeia XX at 37°C and 75 r.p.m., is not more than 15% of the total theophylline after 2 hours of measurement in a buffer solution at pH 7.5. Not more than 35% of the total theophylline is released after a total of 7 hours of measurement and not more than 65% of the total theophylline is released after a total of 13 hours.

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DESCRIPTION

TITLE: "SUSTAINED ABSORPTION PHARMACEUTICAL COMPOSITION"

This invention relates to sustained absorption pharmaceutical compositions and, in particular, to a sustained absorption theophylline composition.

Theophylline (1,3-Dimethylxanthine) has a pharmacological activity similar to that of the other xanthine derivatives, caffeine and theobromine. The diuretic action of theophylline though stronger than that of caffeine is of short duration. Theophylline is a more powerful relaxant of involuntary muscle than either theobromine or caffeine. Theophylline is primarily used as a bronchosphasm relaxant or bronchodilator in bronchosphasm associated with asthma, chronic bronchitis and emphysema.

Theophylline has been found to have a minimum effective plasma concentration of about 5mcg/ml and an average therapeutic concentration of about 10mcg/ml. The therapeutic range of concentration of theophylline is generally regarded in practice as 10-20mcg/ml, levels below 10mcg/ml being ineffective and levels above 20mcg/ml being toxic.

The apparent biological half-life of theophylline has been found to range from 4-9 hours.

Preparations of anhydrous theophylline require a dosage regimen of 150-500mg orally every six hours for adults.

For this reason, a number of slow or sustained release forms of theophylline have been developed and include: THEOGRAD, which is marketed by Abbott Laboratories Limited and comes in 350mg tablets and is administered at a rate of one tablet per 12 hours;

THEO-DUR, marketed by Fisons Limited and which comes in 200mg and 300mg tablets and is administered 12 hourly, initially 200-300mg, increasing by 100-150mg until a sufficient therapeutic effect is obtained; and UNIPHYLLIN UNICONTIN, marketed by Napp Laboratories Limited which comes in 200mg tablets, with three or four tablets being taken as a single daily dose, following initial therapy of two daily given as a once or twice daily dosage with subsequent increments as necessary until a sufficient therapeutic effect is obtained.

With each slow-release form of theophylline the dose is increased until the required therapeutic effect is obtained, this is known as a titration standard.

An effective slow or sustained release form of theophylline suitable for once daily administration must be capable of maintaining the plasma concentration of theophylline within the range of 10-20mcg/ml over 24 hours. Only a product with a Cmax/Cmin at 24 hours ratio of 2:1 or less could maintain levels within this range 24 hours after administration.

It is an object of the present invention to provide a sustained absorption form of theophylline which is suitable for once daily administration and which gives a consistent Cmax/Cmin ratio at 24 hours of 2:1 or less.

Accordingly, the invention provides a sustained absorption theophylline-containing pellet for oral administration, said pellet comprising a core of theophylline or a pharmacological equivalent thereof and an organic acid embedded in a polymeric material in a multi-layer arrangement, and an outer membrane which permits release of the theophylline at a controlled rate in an aqueous medium, said pellet

having a dissolution rate in an aqueous medium which is substantially independent of pH and which when measured in a Basket Assembly according to U.S. Pharmacopoeia XX at 37°C and 75 r.p.m., in a buffer solution at pH 7.5 has the following characteristics:

a) up to 15% of the total theophylline is released during the first two hours of measurement in said assembly;

b) between 15 and 35% of the total theophylline is released after a total of 7 hours of measurement in said assembly;

c) between 45 and 65% of the total theophylline is released after a total of 13 hours of measurement in said assembly; and

d) between 80 and 100% of the total theophylline is released after a total of 24 hours of measurement in said assembly.

As used herein "theophylline" means theophylline or a derivative or salt thereof. Suitable forms of theophylline for use in the pellets according to the invention are anhydrous theophylline, aminophylline, dyphylline, theophylline calcium salicylate and theophylline sodium glycinate.

Preferably, the organic acid is represented by one or more of the following acids: citric acid, tartaric acid, succinic acid, malic acid, ascorbic acid and fumaric acid.

The theophylline and organic acid are preferably present in a ratio of 4:1.

Preferably, the polymeric material in which the theophylline is embedded includes a major proportion of a polymer which is rapidly soluble in water.

The polymeric material may consist solely of a water soluble polymer or, alternatively, it may include a minor proportion of a water insoluble polymer. Suitably, the water soluble and water insoluble polymers will be present in a ratio of 9:1.

The water soluble polymer is suitably hydroxypropylmethylcellulose, polyvinylpyrrolidone or a polymer sold under the trade mark EUDRAGIT RL. Polymers sold under the Trade Mark EUDRAGIT are acrylic resins comprising co-polymers of acrylic and methacrylic acid esters.

The water insoluble polymer is suitably a cellulose ether such as methyl-, ethyl- or propylcellulose, Shellac or a polymer sold under the trade mark EUDRAGIT RS. Shellac is a resinous excretion of the insect Laccifer (Tachardia) Lacca Kerr, order Homoptera, family Coccidae.

The core will suitably have between 20 and 120 layers and is built up in a manner known per se.

Further, preferably, the multi-layer arrangement of theophylline, organic acid and polymeric material will be built up on a central inert core suitably consisting of a non-pareil seed having an average diameter in the range 0.3-0.7mm.

The outer membrane preferably includes a major proportion of a water insoluble polymer.

Further, the outer membrane suitably comprises a major proportion of a water insoluble polymer and a minor proportion of a water soluble polymer, the ratio of water insoluble to water soluble polymer being determined by the inherent solubility characteristics of the polymers selected.

Suitable combinations of water insoluble and water soluble polymers for the outer membrane include: ethylcellulose and hydroxypropylmethylcellulose in a ratio of 9:1; EUDRAGIT RS and EUDRAGIT RL in a ratio of 8:2 and Shellac and polyvinylpyrrolidone in a ratio of 9:1.

The pellets may be filled into hard gelatin capsules or compressed into tablets using a binder and/or hardening agent commonly employed in tabletting such as microcrystalline cellulose sold under the trade mark AVICEL or diisopropylbenzothiazyl-2-sulphenamide sold under the trade mark DIPAC, in such a way that the specific dissolution rate of the pellets is maintained.

The invention will be further illustrated by the following Examples.

EXAMPLE 1

Theophylline-containing pellets were prepared in the following manner.

(a) Powder Blend

Anhydrous theophylline (# 100 mesh)(3,500g), talc (438g) and citric acid (875g) were blended in a standard pharmaceutical blender into a uniform powder.

(b) Polymer Solution

A solution of 5% hydroxypropylmethylcellulose in methanol/methylene chloride, 60:40 was prepared.

(c) Membrane Solution

The membrane solution was prepared from the following ingredients:

One part (by volume) 10% hydroxypropylmethyl-cellulose (15 c.p.s.) in methanol/methylene chloride, 60:40;

Nine parts (by volume) 10% ethylcellulose (50 c.p.s.) in methanol/methylene chloride, 60:40;

Ten parts (by volume) methanol/methylene chloride, 60:40;

Ten parts (by weight) talc;

Diethylphthalate (plasticizer), as required.

Pellet Making Procedure

Step 1. 500g of starch/sugar seeds (0.4 to 0.5mm diameter) were placed in a conventional coating pan and rotation was commenced.

Step 2. The seeds were wetted with sufficient polymer solution (b) to dampen them uniformly.

Step 3. Powder blend (a) was dusted on until no more adhered to the dampened seeds.

Step 4. The powder coated seeds were allowed to dry (5-15 minutes).

Steps 2-4 were repeated until all of the powder (a) had been coated on.

Step 5. The powder coated seeds were sealed with one application of polymer solution (b) and talc.

Step 6. The powder coated seeds were dried at 45-50°C for at least 12 hours.

Step 7. The powder coated seeds were placed in a conventional coating pan and rotation was commenced.

Step 8. A coat of membrane solution (c) was applied to the powder coated seeds and the seeds so coated were allowed to dry. A coat of membrane solution (c) corresponds to 10ml of solution (c) per 1,000g of coated seeds.

Step 9. Two further coats of membrane solution (c) were applied to the coated seeds.

Step 10. The finished pellets were allowed to dry at 45-50°C.

The dried pellets were subjected to a dissolution test as follows:

Apparatus:

A Basket Assembly as described in the United States Pharmacopoeia XX at 37°C and 75 r.p.m.

Buffer:

25ml of 2.0 M potassium chloride and 950ml of water was adjusted to pH 7.5 with either 0.1 N hydrochloric acid or 0.1 N sodium hydroxide and the volume made up to 1,000ml with water.

Sampling Times:

2, 7, 13 and 24 hours.

Method:

1g of finished pellets was placed in the basket of the assembly and rotation was commenced in the buffer. At the sampling times, 1.0ml of the solution was removed and diluted to 50ml with 0.1 M hydrochloric acid. The absorbance of the sample was measured at 270nm in a spectrophotometer.

The absorbance value equivalent to 100% dissolution was determined by grinding 1g of pellets in 0.1 M hydrochloric acid, diluting to 1,000ml with water, further diluting a 1ml sample to 50ml with water and reading at 270nm as above. The percentage dissolution was calculated by division.

Steps 7 to 10 were repeated until the dissolution rate at pH 7.5 was as follows:

2 hours	0- 15%
7 hours	15- 35%
13 hours	45- 65%
24 hours	80-100%

EXAMPLE 2

Theophylline-containing pellets were prepared in the following manner.

(a) Powder Blend

Anhydrous theophylline (# 100 mesh)(3,500g), talc (438g) and tartaric acid (875g) were blended in a standard pharmaceutical blender into a uniform powder.

(b) Polymer Solution

A solution of nine parts 6.25% EUDRAGIT RL in isopropanol/acetone, 60:40 and one part 6.25% EUDRAGIT RS in isopropanol/acetone, 60:40 was prepared.

(c) Membrane Solution

The membrane solution was prepared from the following ingredients:

Two parts (by volume) 5% EUDRAGIT RL in isopropanol/acetone, 60:40;

Eight parts (by volume) 5% EUDRAGIT RS in isopropanol/acetone, 60:40;

Ten parts (by volume) isopropanol/acetone, 60:40;

Ten parts (by weight) talc;

Diethylphthalate (plasticizer), as required.

Pellet Making Procedure

Steps 1-4 were carried out as in Example 1.

Steps 2-4 were repeated until all of the powder (a) had been coated on.

Step 5. The powder coated seeds were sealed with two applications of polymer solution (b) and talc.

Steps 6-8 were carried out as in Example 1. As in the case of Example 1 a coat of membrane solution (c) corresponds to 10ml of solution (c) per 1,000g of coated seeds.

Step 9. One further coat of membrane solution (c) was applied to the coated seeds.

Step 10. The finished pellets were allowed to dry at 45-50°C.

The dried pellets were subjected to a dissolution test as described in Example 1 and Steps 7-10 were repeated until the desired dissolution rate at pH 7.5 was obtained.

EXAMPLE 3

Theophylline-containing pellets were prepared in the following manner.

(a) Powder Blend

Anhydrous theophylline (# 100 mesh)(3,500g), talc (438g) and succinic acid (875g) were blended in a standard pharmaceutical blender into a uniform powder.

(b) Polymer Solution

A solution of 10% polyvinylpyrrolidone in isopropanol was prepared.

(c) Membrane Solution

The membrane solution was prepared from the following ingredients:

One part (by volume) 20% polyvinylpyrrolidone (Kollidon K-30) in isopropanol;

Nine parts (by volume) 33% Shellac (dewaxed) in ethanol;

Ten parts (by volume) isopropanol;

Ten parts (by weight) talc;

Diethylphthalate (plasticizer), as required.

Pellet Making Procedure

Steps 1-4 were carried out as in Example 1.

Steps 2-4 were repeated until all of the powder (a) had been coated on.

Steps 5-10 were carried out as in Example 1.

The dried pellets were then subjected to a dissolution test as described in Example 1 above. In addition, the dissolution rate was also measured at pH 3.0 and pH 6.0. Steps 7-10 were repeated until a satisfactory dissolution rate was obtained at each pH. A total of 20 coats of membrane solution (c) was applied before the required dissolution rate was obtained.

Table 1 gives the percentage dissolution observed at each pH after 15, 17, 18 and 20 coats of membrane solution (c) had been applied.

TABLE 1

Membrane Coats Applied	Time (h)	Dissolution (%) pH 3.0	6.0	7.5
15	2	14	17	17
	7	60	66	68
	13	95	98	100
	24	100	100	100
17	2	10	10	11
	7	40	43	45
	13	76	80	84
	24	100	100	100
18	2	6	8	7
	7	35	42	39
	13	67	73	71
	24	100	100	100
20	2	5	7	7
	7	25	28	30
	13	52	56	58
	24	86	90	94

It will be observed from Table 1 that the percentage dissolution at pH 3.0 and 6.0 at each sampling time were within 8% of the corresponding figure obtained at pH 7.5. Accordingly, it will be appreciated that the dissolution rate of the pellets according to the invention is substantially pH independent.

Fig. 1 is a graph of percentage dissolution versus time of pellets according to the invention. Curve B shows the maximum percentage dissolution per unit time and curve A the minimum percentage dissolution per unit time permissible to achieve the desired plasma concentration Cmax/Cmin at 24 hours of 2:1 or less.

Fig. 2 is a graph of plasma levels (mcg/ml) versus time after administration (hours) for pellets prepared according to Example 3 (o) compared with two sustained release forms of theophylline currently on the market, namely THEO-DUR tablets (*) and UNIPHYLLIN UNICONTIN tablets (+).

The graphs of Fig. 2 were drawn from the mean values obtained for six subjects according to the data listed in Tables 2, 3 and 4.

TABLE 2

Sustained-absorption theophylline pellets prepared according to Example 3

Blood level study results - Summary of pharmacokinetic data

Plasma Levels (mcg/ml)

	HOURS AFTER ADMINISTRATION															
SUBJ	0.00	3.00	4.00	5.00	6.00	8.00	10.00	11.00	12.00	13.00	14.00	16.00	24.00	36.00	48.00	AUC**
1	0.00	1.67	2.64	3.38	4.24	6.70	6.86	6.71	7.02	6.04	6.36	6.62	6.36	3.69	1.64	219.54
2	0.00	1.12	1.76	3.04	5.06	5.99	6.86	7.62	7.38	7.15	7.49	6.59	4.13	1.36	0.51	163.91
3	0.00	1.37	1.85	2.95	3.82	4.41	4.44	4.72	5.25	5.31	4.32	5.30	4.82	1.10	0.00	138.41
4	0.00	1.59	2.10	2.57	4.85	7.05	8.38	8.38	8.31	9.00	7.99	8.22	6.07	1.84	0.61	207.01
5	0.00	1.34	1.83	2.88	4.10	4.91	5.29	4.71	4.53	4.37	4.40	4.19	3.30	1.10	0.00	118.65
6	0.00	1.34	6.97	13.83	13.06	12.58	10.77	11.30	10.37	9.27	8.43	6.23	2.90	1.18	0.00	202.28
MEAN	0.00	1.41	2.86	4.78	5.86	6.94	7.10	7.24	7.14	6.86	6.50	6.19	4.60	1.71	0.46	174.97
ST DEV	0.00	0.20	2.04	4.44	3.56	2.94	2.26	2.49	2.11	1.99	1.79	1.36	1.42	1.01	0.64	40.96
*CV (%)	0.00	14.07	71.37	93.06	60.81	42.41	31.85	34.37	29.54	28.98	27.62	21.98	30.93	58.92	139.27	23.41
MAX	0.00	1.67	6.97	13.83	13.06	12.58	10.77	11.30	10.37	9.27	8.43	8.22	6.36	3.69	1.64	219.54
MIN	0.00	1.12	1.76	2.57	3.82	4.41	4.44	4.71	4.53	4.37	4.32	4.19	2.90	1.10	0.00	118.65

MEAN OF CV VALUES AT SAMPLE POINTS	NUMBER OF ZERO BLOOD LEVELS	NUMBER OF POOR ABSORBERS ** <10% AUC
48.94	3	0

Table 2 continued

	HOURS COVER AT FOUR BLOOD LEVELS				PEAKING	PEAK	C(MAX)/C(MIN)
SUBJ	0.00	5.00	10.00	20.00	TIME	HEIGHT	AT 24.00 HOURS
1	48.00	23.49	0.00	0.00	12.00	7.02	1.10
2	48.00	15.20	0.00	0.00	11.00	7.62	1.85
3	48.00	7.40	0.00	0.00	13.00	5.31	1.10
4	48.00	20.90	0.00	0.00	13.00	9.00	1.48
5	48.00	2.03	0.00	0.00	10.00	5.29	1.60
6	48.00	15.30	7.89	0.00	5.00	13.83	4.77
MEAN	48.00	14.05	1.32	0.00	10.67	8.01	1.98
ST DEV	0.00	8.10	3.22	0.00	3.01	3.18	1.40
CV(%)	0.00	0.58	2.45	0.00	0.28	0.40	0.70
BASED ON MEAN BLOOD LEVEL CURVE							
MEAN	48.00	16.77	0.00	0.00	11.00	7.24	1.58

* Coefficient of variation

** Area under the curve.

TABLE 3

Theo-Dur SR tablets

Blood level study results - Summary of pharmacokinetic data

Plasma Levels (mcg/ml)

	HOURS AFTER ADMINISTRATION															
SUBJ	0.00	3.00	4.00	5.00	6.00	8.00	10.00	11.00	12.00	13.00	14.00	16.00	24.00	36.00	48.00	AUC**
1	0.00	5.70	7.48	9.05	10.26	13.84	10.64	9.82	9.21	8.82	9.23	7.29	4.33	2.05	0.89	238.34
2	0.00	3.33	5.62	7.06	8.30	7.99	8.01	7.29	6.66	6.80	6.59	5.53	2.63	1.18	0.50	161.53
3	0.00	3.31	3.88	5.13	6.82	7.37	8.66	8.55	8.15	7.99	8.09	7.05	3.97	1.11	0.00	178.68
4	0.00	4.38	4.56	6.69	7.88	10.26	11.61	12.91	12.39	10.58	9.98	8.60	4.32	0.92	0.00	217.85
5	0.00	3.65	4.49	5.61	6.95	8.05	7.29	5.91	5.75	4.72	4.37	3.30	0.96	0.00	0.00	103.89
6	0.00	5.09	4.75	5.39	6.40	8.60	8.17	7.37	7.24	7.28	6.26	5.90	2.72	0.96	0.00	158.87
MEAN	0.00	4.24	5.13	6.49	7.77	9.35	9.06	8.64	8.23	7.70	7.42	6.28	3.16	1.04	0.23	176.53
ST DEV	0.00	0.99	1.28	1.47	1.41	2.41	1.68	2.47	2.36	1.97	2.08	1.82	1.32	0.66	0.38	47.64
*CV(%)	0.00	23.36	24.97	22.60	18.15	25.76	18.59	28.59	28.67	25.65	28.02	29.01	41.77	63.21	163.81	26.98
MAX	0.00	5.70	7.48	9.05	10.26	13.84	11.61	12.91	12.39	10.58	9.98	8.60	4.33	2.05	0.89	238.34
MIN	0.00	3.31	3.88	5.13	6.40	7.37	7.29	5.91	5.75	4.72	4.37	3.30	0.96	0.00	0.00	102.89

MEAN OF CV VALUES AT SAMPLE POINTS	NUMBER OF ZERO BLOOD LEVELS	NUMBER OF POOR ABSORBERS <10% AUC
38.73	5	0

Table 3 continued

	HOURS COVER AT FOUR BLOOD LEVELS				PEAKING	PEAK	C(MAX)/C(MIN)
SUBJ	0.00	5.00	10.00	20.00	TIME	HEIGHT	AT 24.00 HOURS
1	48.00	19.56	5.00	0.00	8.00	13.84	3.20
2	48.00	13.73	0.00	0.00	6.00	8.30	3.16
3	48.00	16.43	0.00	0.00	10.00	8.66	2.18
4	48.00	18.52	6.19	0.00	11.00	12.91	2.99
5	36.00	8.27	0.00	0.00	8.00	8.05	8.39
6	48.00	14.19	0.00	0.00	8.00	8.60	3.16
MEAN	46.00	15.12	1.86	0.00	8.50	10.06	3.85
ST DEV	4.90	4.07	2.91	0.00	1.76	2.59	2.26
CV(%)	0.11	0.27	1.56	0.00	0.21	0.26	0.59
BASED ON MEAN BLOOD LEVEL CURVE							
MEAN	48.00	15.42	0.00	0.00	8.00	9.35	2.96

* Coefficient of variation

** Area under the curve

TABLE 4

Uniphylline Unicontin

Blood level study results - Summary of pharmacokinetic data

Plasma Levels (mcg/ml)

	HOURS AFTER ADMINISTRATION															
SUBJ	0.00	3.00	4.00	5.00	6.00	8.00	10.00	11.00	12.00	13.00	14.00	16.00	24.00	36.00	48.00	AUC**
1	0.00	5.70	6.89	8.35	9.52	10.67	10.42	9.55	10.17	9.45	9.28	8.68	8.50	3.26	1.49	297.44
2	0.00	4.98	5.64	5.81	5.14	4.82	5.58	5.22	5.10	5.30	5.05	4.49	2.20	0.74	0.00	123.65
3	0.00	8.87	11.88	12.59	9.79	8.26	7.26	7.14	6.65	7.58	6.76	6.53	4.47	1.13	0.00	206.72
4	0.00	4.99	6.20	6.10	6.85	5.72	8.03	8.28	8.46	7.92	8.39	7.00	4.68	2.01	0.84	204.24
5	0.00	3.87	3.90	5.15	6.16	5.34	4.69	4.29	4.02	3.58	3.41	2.69	1.80	0.00	0.00	92.20
6	0.00	5.85	6.12	6.79	6.80	9.71	11.22	11.47	10.68	10.19	9.63	7.36	3.08	0.96	0.00	196.96
MEAN	0.00	5.71	6.77	7.47	7.38	7.42	7.87	7.66	7.51	7.34	7.09	6.13	4.12	1.35	0.39	186.87
ST DEV	0.00	17.0	2.70	2.74	1.87	2.47	2.59	2.69	2.71	2.50	2.48	2.17	2.44	1.14	0.64	72.09
*CV(%)	0.00	29.76	39.84	36.67	25.37	33.28	32.89	35.06	36.09	34.09	34.99	35.36	59.20	84.32	163.71	38.58
MAX	0.00	8.87	11.88	12.59	9.79	10.67	11.22	11.47	10.68	10.19	9.63	8.68	8.50	3.26	1.49	297.44
MIN	0.00	3.87	3.90	5.15	5.14	4.82	4.69	4.29	4.02	3.58	3.41	2.69	1.80	0.00	0.00	92.20

MEAN OF CV VALUES AT SAMPLE POINTS	NUMBER OF ZERO BLOOD LEVELS	NUMBER OF POOR ABSORBERS <10% AUC
48.62	5	0

Table 4 continued

	HOURS COVER AT FOUR BLOOD LEVELS				PEAKING	PEAK	C(MAX)/C(MIN)
SUBJ	0.00	5.00	10.00	20.00	TIME	HEIGHT	AT 24.00 HOURS
1	48.00	29.38	4.16	0.00	8.00	10.67	1.26
2	48.00	9.55	0.00	0.00	5.00	5.81	2.64
3	48.00	20.25	2.55	0.00	5.00	12.59	2.82
4	48.00	19.89	0.00	0.00	12.00	8.46	1.81
5	36.00	4.17	0.00	0.00	6.00	6.16	3.42
6	48.00	17.85	4.96	0.00	11.00	11.47	3.72
MEAN	46.00	16.85	1.94	0.00	7.83	9.19	2.61
ST DEV	4.90	8.87	2.27	0.00	3.06	2.83	0.94
CV(%)	0.11	0.53	1.17	0.00	0.39	0.31	0.36
BASED ON MEAN BLOOD LEVEL CURVE							
MEAN	48.00	17.87	0.00	0.00	10.00	7.87	1.91

* Coefficient of variation

** Area under the curve

It was found that a 600mg single dose of theophylline pellets prepared according to Example 3 in tablet form had a similar plasma level AUC (area under the curve)(175mcg h/ml) as a 600mg single dose of each of THEO-DUR (176.5mcg h/ml) and UNIPHYLLIN UNICONTIN (186.9mcg h/ml).

The theophylline prepared according to Example 3 had the lowest peak plasma level (Cmax) at the latest peak time (tmax) as shown in Table 5.

TABLE 5

	Cmax(mcg/ml)	tmax(h)
Composition of Example 3	8.0	10.7
THEO-DUR	10.1	8.5
UNIPHYLLIN UNICONTIN	9.2	7.8

Furthermore, the theophylline prepared according to Example 3 showed the lowest single-dose peak to trough plasma concentration ratio (Cmax/Cmin at 24 hours); Composition according to Example 3 = 1.98; THEO-DUR = 3.85; and UNIPHYLLIN UNICONTIN = 2.61.

In terms of variability, the theophylline prepared according to Example 3 showed the lowest inter subject variability in plasma level AUC (area under the curve); Composition according to Example 3 % CV = 23.4; THEO-DUR % CV = 27.0; and UNIPHYLLIN UNICONTIN % CV = 38.6.

It will be appreciated from the foregoing description that the pellets according to the invention are more readily absorbed than conventional sustained release forms of theophylline with a similar rate of release.

CLAIMS:-

1. A sustained absorption theophylline-containing pellet for oral administration, characterised in that the pellet has a core of theophylline or a pharmacological equivalent thereof and an organic acid embedded in a polymeric material in a multi-layer arrangement and an outer membrane which permits release of the theophylline at a controlled rate in an aqueous medium, said pellet having a dissolution rate in an aqueous medium which is substantially independent of pH and which when measured in a basket assembly according to U.S. Pharmacopoeia XX at 37°C and 75 r.p.m., in a buffer solution at pH 7.5 has the following characteristics:

a) up to 15% of the total theophylline is released during the first two hours of measurement in said assembly;
b) between 15 and 35% of the total theophylline is released after a total of 7 hours of measurement in said assembly;
c) between 45 and 65% of the total theophylline is released after a total of 13 hours of measurement in said assembly; and
d) between 80 and 100% of the total theophylline is released after a total of 24 hours of measurement in said assembly.

2. A pellet according to Claim 1, wherein the core contains as active ingredient anhydrous theophylline aminophylline, dyphylline, theophylline calcium salicylate or theophylline sodium glucinate.

3. A pellet according to Claim 1 or 2, wherein the organic acid is citric acid, tartaric acid, succinic acid, malic acid, ascorbic acid or fumaric acid or a mixture thereof.

4. A pellet according to any one of Claims 1-3, characterised in that the polymeric material of the core includes a major proportion of a polymer which is rapidly soluble in water, especially hydroxypropylmethylcellulose, polyvinylpyrrolidone or EUDRAGIT RL.

5. A pellet according to any one of Claims 1-4, which includes a minor proportion of a water-insoluble polymer, especially methylcellulose, ethylcellulose, propylcellulose, Shellac or EUDRAGIT RS, the water-soluble and water-insoluble polymers being present in a ratio of 9:1.

6. A pellet according to any preceding claim, wherein the multi-layer arrangement of theophylline, organic acid and polymeric material is built up on an inert core in a manner known per se, the core preferably having between 20 and 120 layers.

7. A pellet according to any preceding claim, wherein the outer membrane includes a major proportion of a water-insoluble polymer and a minor proportion of a water-soluble polymer, the ratio of water-insoluble to water-soluble polymer being determined by the inherent solubility characteristics of the polymers selected.

8. A pellet according to any preceding claim characterised in that the outer membrane consists of: ethylcellulose and hydroxypropylcellulose in a ratio of 9:1; EUDRAGIT RS and EUDRAGIT RL in a ratio of 8:2; or Shellac and polyvinylpyrrolidone in a ratio of 9:1.

9. A capsule or tablet comprising pellets according to any one of the preceding claims.

10. A process for the production of a pellet according to any one of claims 1-8 comprising forming a core of theophylline or a pharmacological equivalent thereof and an organic acid embedded in a polymeric material in a multi-layer arrangement and enclosing the core in an outer membrane which permits release of the theophylline in the manner set out in claim 1.

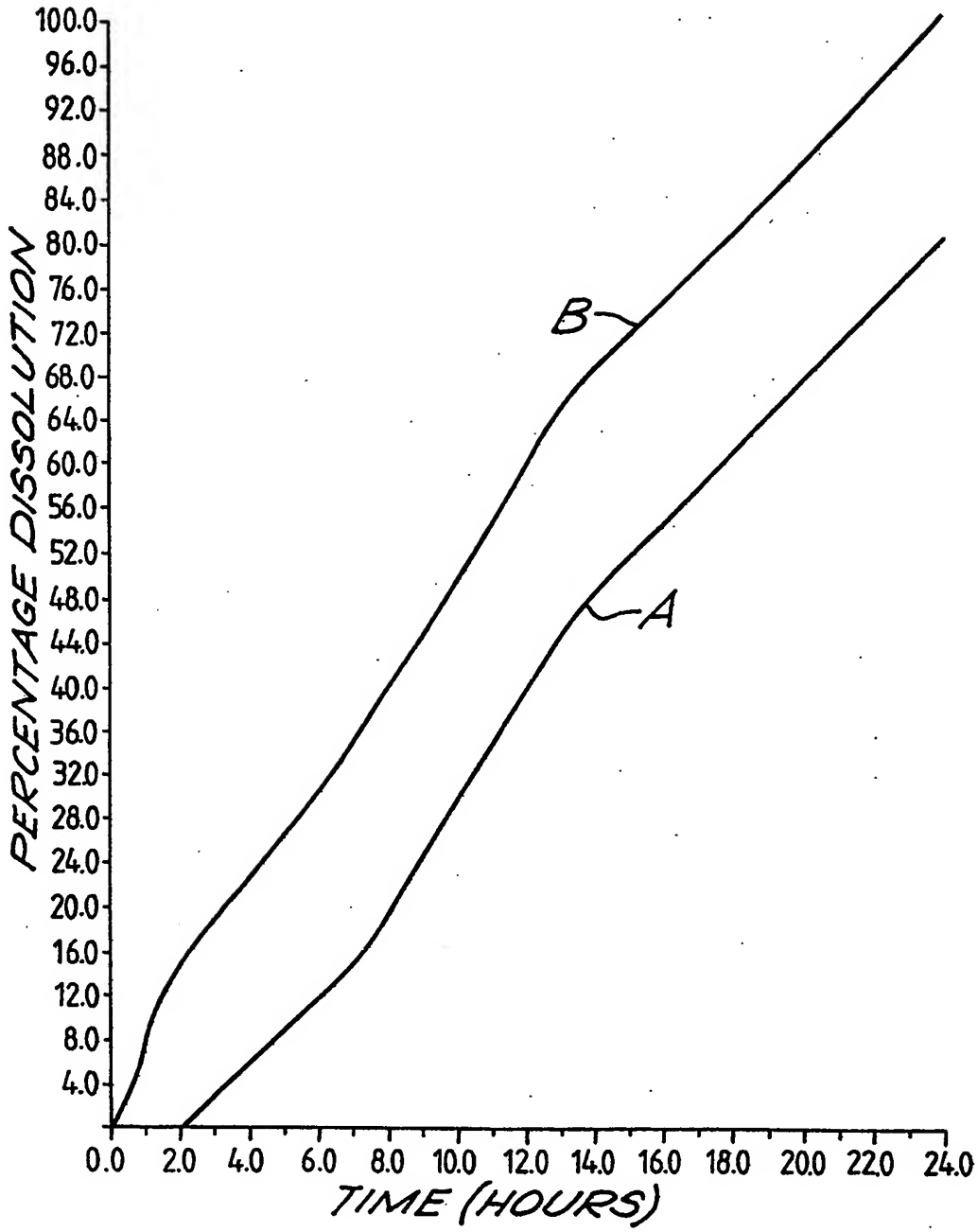
PERCENTAGE DISSOLUTION
100.0
96.0
92.0
88.0
84.0
80.0
76.0
72.0
68.0
64.0
60.0
56.0
52.0
48.0
44.0
40.0
36.0
32.0
28.0
24.0
20.0
16.0
12.0
8.0
4.0
0.0
2.0
4.0
6.0
8.0
10.0
12.0
14.0
16.0
18.0
20.0
22.0
24.0
TIME (HOURS)
B
A

FIG.1.

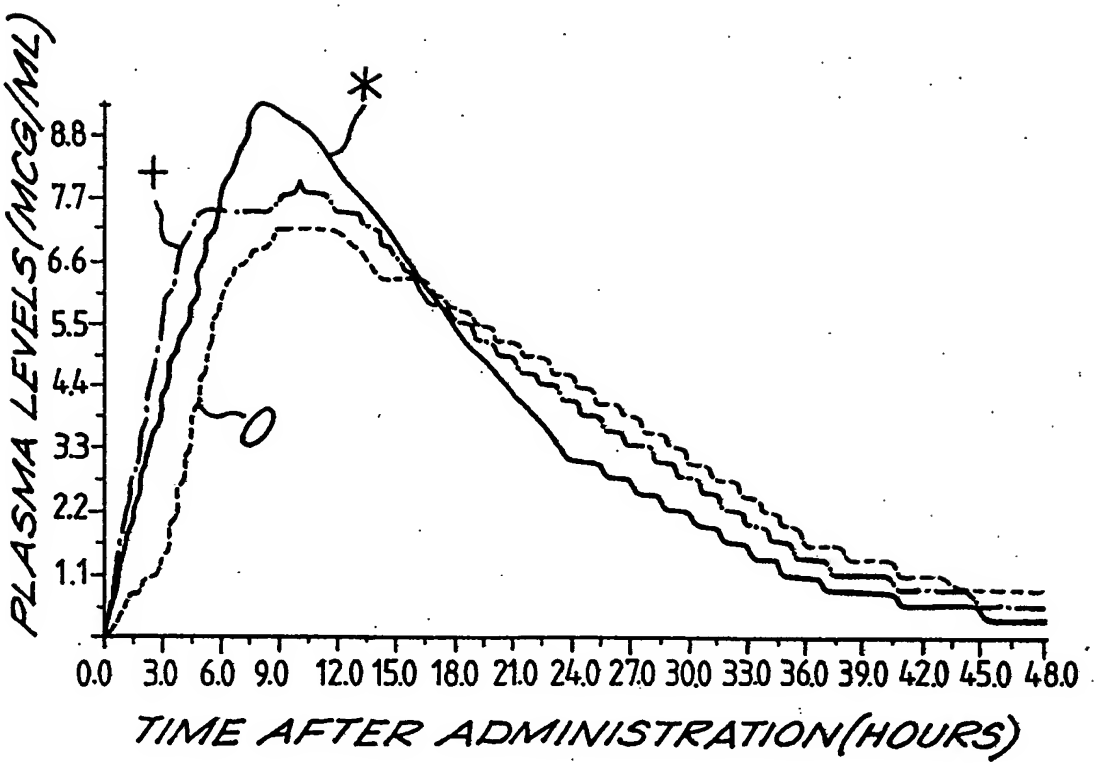
PLASMA LEVELS (MCG/ML)
8.8
7.7
6.6
5.5
4.4
3.3
2.2
1.1
0.0 3.0 6.0 9.0 12.0 15.0 18.0 21.0 24.0 27.0 30.0 33.0 36.0 39.0 42.0 45.0 48.0
TIME AFTER ADMINISTRATION (HOURS)
+
*
O

FIG.2.